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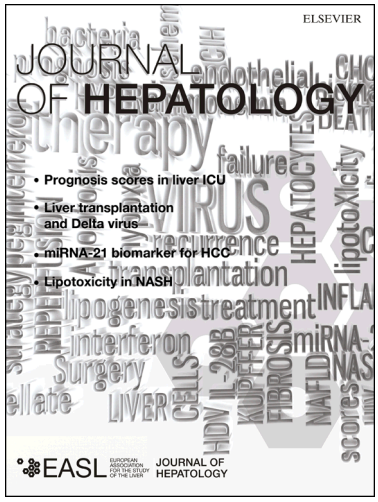

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High Hepatic and Extrahepatic Mortality and Low Treatment Uptake in HCV-coinfected Persons in the Swiss HIV Cohort Study between 2001 and 2013

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ALT, alanine aminotransferase

AST, aspartate aminotransferase

ART, antiretroviral therapy

DAA, direct-acting antiviral drug

HBV, hepatitis B virus

HCV, hepatitis C virus

IDU, intravenous drug user

IFN, interferon

MSM, men who have sex with men

pegIFN, pegylated interferon

PY, person years

RBV, ribavirin

SHCS, Swiss HIV Cohort Study

SVR, sustained virological response

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Author's contribution:

HK, BL, RW and AR concepted and designed the study. HK, MC, JA, AB, MS, EB, RW and AR were responsible for the data acquisition. BL analyzed the data. All authors interpreted the data. HK and AR prepared the paper. All authors read and approved the final manuscript.

ABSTRACT

Background & Aims: The landscape of HCV treatments is changing dramatically. At the beginning of this new era, we highlight the challenges for HCV-therapy by assessing the long-term epidemiological trends in treatment uptake, efficacy and mortality among HIV/HCV-coinfected people since the availability of HCV therapy.

Methods: We included all SHCS participants with detectable HCV RNA between 2001 and 2013. To identify predictors for treatment uptake uni- and multivariable Poisson regression models were applied. We further used survival analyses with Kaplan-Meier curves and Cox regression with drop-out as competing risk.

Results: Of 12,401 participants 2107 (17%) were HCV RNA positive. Of those, 636 (30%) started treatment with an incidence of 5.8/100 person years (PY) (95% CI 5.3-6.2). Sustained virological response (SVR) with pegylated interferon/ribavirin was achieved in 50% of treated patients, representing 15% of all participants with replicating HCV infection. 344 of 2107 (16%) HCV RNA positive persons died, 59% from extrahepatic causes. Mortality/100 PY was 2.9 (95% CI 2.6-3.2) in untreated patients, 1.3 (1.0-1.8) in those treated with failure, and 0.6 (0.4-1.0) in patients with SVR. In 2013, 869/2107 (41%) participants remained HCV RNA positive.

Conclusions: Over the last 13 years HCV treatment uptake was low and by the end of 2013, a large number of persons remain to be treated. Mortality was high, particularly in untreated patients, and mainly due to non-liver related causes. Accordingly, in HIV/HCV-coinfected patients, integrative care including the diagnosis and therapy of somatic and psychiatric disorders is important to achieve mortality rates similar to HIV-monoinfected patients.

INTRODUCTION

The treatment of hepatitis C virus (HCV) infection in HIV-infected patients has changed dramatically in the last decades. Before 1990, HCV infection was incurable. Subsequently, sustained viral response (SVR) was only about 10% with interferon monotherapy [1]. After 2000, and until recently, the pegylated interferon and ribavirin (pegIFN/RBV) combination therapy improved outcome substantially, but still resulted in modest SVR of 14-29% for genotype 1, and 44-73% for genotypes 2 or 3 [2-4]. Although successful treatment of chronic HCV-infection decreased liver-specific and all-cause mortality [5, 6], rates of treatment uptake in the HIV-coinfected population were low [7]. Barriers to start treatment included comorbid medical and psychiatric conditions, active substance abuse with the inability to adhere to complex HCV treatment regimens, expected adverse effects of or contraindications for HCV combination therapy, and uncontrolled HIV disease (reviewed in [7]).

With the availability of direct-acting antivirals (DAAs), the landscape of HCV treatment is changing rapidly. New treatment options with high cure rates for HIV/HCV-coinfected patients are now available or will be approved shortly. At the beginning of this new era, documentation of the long-term epidemiological trends, treatment uptake, outcome and mortality of HCV-infections is important to adequately assess the impact of new therapies. Moreover, physicians and public health authorities need information on the proportion of patients with replicating HCV-infection, on HCV genotype distribution and on liver-related complications in representative populations. This information is key to define the most urgent treatment priorities, and to optimally invest the available resources in order to reduce HCV-related mortality in HIV-infected patients.

The Swiss HIV Cohort Study (SHCS) offers an ideal platform to study the natural course of HCV-infection and long-term influence of HCV treatments in a nation-wide

representative population of HIV-infected patients. We aimed to i), assess the changes in epidemiology, clinical course and therapy of HCV-infections between 2001 and 2013, and ii), to characterize the population who remains eligible for the new HCV treatment options by the end of 2013.

PATIENTS AND METHODS

Swiss HIV Cohort Study

The SHCS is an ongoing, prospective cohort study that continuously enrolls and observes HIV-infected adults at 5 university outpatient clinics, 2 large district hospitals, affiliated regional hospitals, and private practices, since 1988. This nationwide cohort covers 69% of all patients living with AIDS, and 75% of persons receiving antiretroviral therapy (ART) in Switzerland [8, 9]. Demographic, clinical and laboratory data are collected at registration and every 6 months thereafter using a standard protocol. The protocol was approved by local ethical review boards, and written informed consent was obtained from all participants.

The indication for HCV therapy and treatment monitoring is provided by HIV- and HCV-trained infectious diseases specialists in the same clinical setting as HIV therapy.

Laboratory measurements and data collection

All SHCS participants are routinely screened for HCV antibodies at study entry. Since 1998, serology was repeated every second year of follow-up in participants with previously negative results. Starting routinely in 2002, quantitative HCV RNA measurements and HCV genotype determination were undertaken in HCV-seropositive persons.

In addition to the information retrieved from the SHCS database, detailed information on HCV-infection, on treatment history and outcomes was obtained by retrospective chart review using a structured questionnaire. Deaths were classified as liver-related (including cirrhosis and liver cancer), HIV/AIDS, cardiovascular, non-liver cancer, sepsis due to any cause (including bacterial and candida septicemia, endocarditis, pneumonia, bacterial meningitis), drug-related, and other causes. All events neither related to HCV infection nor to other liver diseases were classified as extrahepatic events. Events involving other organs than the liver, but clearly associated with liver cirrhosis, including variceal hemorrhage and hepatorenal syndrome, were classified as liver-related.

Patients' selection

All SHCS participants with at least one study visit between 1 January 2001, the date when pegIFN became available for HIV/HCV-coinfected patients in Switzerland, and 31 December 2013 were included in these analyses. Patients treated with standard IFN (with or without RBV) were excluded (n=22).

Definitions

HCV treatment outcomes were defined as SVR, relapse, or nonresponse, according to standard definitions [10]. SVR was defined as at least one negative HCV RNA test ≥12 weeks after the end of treatment [11]. Patients without an HCV RNA test after the end of treatment were classified as nonresponders if their HCV RNA remained positive during treatment (n=8), and were excluded if their HCV RNA was undetectable at the end of treatment or at the last on-treatment test (n=6), or if they had no available on-treatment HCV RNA value (n=22). A treatment course was considered terminated if pegIFN was discontinued for ≥30 days.

Liver fibrosis stage was derived from liver biopsy using the METAVIR scoring system [12], or alternatively from transient elastography (Fibroscan®, Echosens S.A.S.U., Paris, France), with cut-off values of ≥9.5 kPa for Metavir ≥F3 and >12.5 kPa for Metavir F4 [13]. Liver biopsy was not mandatory prior to the initiation of HCV treatment. Patients were selected for liver biopsy by physicians' choice and patient willingness. Use of transient elastography started in 2005 in Switzerland. The two non-invasive biomarkers of liver fibrosis FIB-4 and APRI were calculated as follows: FIB-4: (age x AST)/[platelet count (10^9cells/L) x sqr(ALT)], and APRI: [(AST/ULN)/platelet count] x 100. A FIB-4 value >3.25, and an APRI score >1.5 is indicative for fibrosis stage F3/4 [14, 15]. Undetectable HIV RNA was defined by values <50 copies/mL. Hepatitis B virus (HBV) infection was defined by a positive hepatitis B surface antigen or detectable viral load. Data on alcohol use was collected by a questionnaire on self-reported alcohol consumption. Severe alcohol abuse was defined according to the WHO definition (female >40g/d, male >60g/d). Psychiatric disorder was defined by treatment with psychotropic drugs, and after 2008 by a diagnosis of depression.

Statistical Analysis

Treatment uptake analyses

For the analyses of treatment uptake, all HCV-seropositive SHCS participants with positive HCV RNA and at least 2 visits were included. They were followed up to their last visit, death, or the date of starting HCV therapy. We used univariable and multivariable Poisson regression models to identify predictors for treatment uptake. Baseline was defined as 1 January 2001 or the date of the first detectable HCV RNA whichever occurred later. Fixed covariables included age, sex, HIV transmission risk group, HCV genotype, HCV RNA level, CD4 cell count, ART with or without HIV RNA

<50 copies/mL, psychiatric disorder, type of health care provider and calendar period (2001-2004, 2005-2007, 2008-2010, 2011-2013). Characteristics of treated patients at treatment start and untreated patients at last follow-up were compared using Fisher's exact tests for categorical and Wilcoxon rank-sum tests for continuous variables.

Treatment efficacy analyses

Treatment outcomes were analyzed separately for genotype 1 and 4, respectively 2 and 3, because of the different SVR rates by genotype. Early therapies in acute HCV infections and DAA treatment regimens (in Switzerland available after November 2011, n=57) were not considered for the analyses of treatment outcome. In patients with multiple treatment courses, only the first course was evaluated for treatment uptake and outcome. Time trends were analyzed using non-parametric tests for trend.

Survival analyses

Survival analyses of participants with at least two follow-up visits were performed using Kaplan-Meier curves and Cox regression with drop-out as competing risk. Baseline was defined as the date of the first visit after 1 January 2001.

We used Stata/SE 13.1 (StataCorp, College Station, Texas, USA) for all analyses.

RESULTS

Study population

Of 12'401 SHCS participants followed between 1 January 2001 and 31 December 2013, 2956 (23.8%) were HCV antibody positive, and 2107 (17.0%) were HCV RNA positive (Figure 1). In 415 patients HCV RNA was not available (Figure 1). Of those, 42.0% died and 39.5% left the cohort in the first years after the approval of pegIFN/RBV therapy in Switzerland, in a time period where HCV RNA was not

collected systematically. HCV RNA tested vs HCV RNA untested patients did not differ regarding sex, age, and HIV transmission mode (all P>0.1). HCV RNA positive patients had in 43% genotype 1, in 3% genotype 2, in 25% genotype 3, in 16% genotype 4, and in 0.1% genotype 6 infections. The proportion of men was 69% and median age at registration was 33 years. The distribution of HIV transmission group was 69% intravenous drug users (IDU), 16% heterosexuals and 12% men who have sex with men (MSM). The treatment providers were university centers (62%), affiliated hospitals (12%), and private HIV practitioners (27%) (Table 1). Of 2519 HCV seropositive patients with available HCV RNA values 491 (19.5%) cleared HCV spontaneously.

HCV treatment uptake

The 2107 HCV RNA positive participants contributed to 10,764 person years (PY). 1471 (70%) participants never received HCV therapy, whereas 636 (30%) started treatment between 2001 and 2013, resulting in an overall incidence of 5.8/100 PY (95% CI 53-6.2); 6.6 (5.7-7.6) before 2004, 5.2 (4.4-6.1) between 2005-2007, 5.3 (4.5-6.2) between 2008-2010, and 6.1 (5.1-7.2) between 2011-2013. The incidence of treatment start was 5.3 (4.7-6.0) in genotype 1, 5.0 (3.0-8.1) in genotype 2, 9.7 (8.5-11.0) in genotype 3, and 3.4 (2.7-4.3) in genotype 4 infections.

Characteristics of HCV treated and untreated participants at date of treatment start or date of last follow-up visit are displayed in Table 1. Untreated patients missed more appointments during the follow-up period (FUP). Mean number of missed appointments/year during FUP for untreated vs treated patients were 0.05 and 0.02, respectively (p <0.001). In the multivariable model, predictors for treatment uptake were genotype 3, younger age, MSM, CD4 cell count >200 cells/µL, absence of

psychiatric disorders, and being under the care of an HIV practitioner. Treatment uptake did not change significantly between time periods (Table 2).

Of 636 treated patients, 11% were treated twice, and 2% had ≥3 treatment cycles. 144 (6.8%) of 2107 HCV RNA positive infections were incident infections. Of these, 39 (27%) were treated early within 6 months after first HCV diagnosis.

Treatment outcome

Between 2001 and 2013, SVR was achieved in 321 of 636 (50.5%) treated participants. In chronic therapy-naïve genotype 1 and 4 infections, treated with pegIFN/RBV, overall SVR was 35.2% (95/270); 32.6% before 2005, 23.4% between 2005-2007, 44.3% between 2008-2010, and 54.6% between 2011-2013 (test for trend, P=0.03). In genotype 2 and 3 infections, overall SVR was 68.4% (167/244); and 63.9%, 72.5%, 72.3%, and 67.7% in the different time periods, respectively (P=0.37). Liver transplantation because of HCV-associated end-stage liver disease was performed in 11 coinfected participants.

Mortality

Mortality (per 100 PY) was 2.9 (95% CI 2.6-3.2) in HCV-coinfected participants who were not HCV treated, 1.3 (1.0-1.8) in treated patients with treatment failure, 0.6 (0.4-1.0) in treated patients with SVR, and 0.9 (0.8-1.0) in participants without HCV-coinfection. This pattern was confirmed in Cox regression with drop-out as competing risk, resulting in subhazard ratios of 3.0 (95% CI 2.6-3.4, P<0.001) for untreated, 1.6 (1.2-2.2, P=0.001) for treated patients without SVR, and 0.8 (0.5-1.3, P=0.3) for patients with SVR, compared with participants not coinfected with HCV. Subhazard ratio for treated patients without SVR vs. SVR was 2.1 (1.2-3.6, P=0.009), and for untreated vs. treated participants with failure 1.9 (1.4-2.5, P<0.001) (Figure 2).

Baseline characteristics of HCV negative, HCV positive treated and untreated patients are shown in the supplementary Table S1.

Among the HCV untreated participants, a total of 295/1471 (20.1%) died. Causes of death were liver-related (38.0%), HIV/AIDS (17.6%), sepsis (15.0%), and cardiovascular diseases (12.4%) in 193 participants with known causes of death. In the treated group 49/636 (7.7%) patients died; causes were liver-related (59.4%), sepsis (19.4%), HIV-AIDS (8.3%), and cardiovascular diseases (5.6%) in 32 patients with known causes of death.

Temporal changes in the characteristics of the HCV-positive population

Figure 3A shows temporal changes in outcomes of all SHCS participants with active HCV infection between 2001 and 2013. Figure 3B depicts the genotype distribution among SHCS participants with a replicating HCV infection over time. The proportion of genotype 1 treatment naïve participants decreased from 45.3% in 2001 to 37.5% in 2013, and HCV replicating treatment experienced patients increased from 2.1% to 15.4%. Genotype 3 treatment naïve individuals decreased from 29.5% to 14.7%, and HCV-replicating treatment experienced increased from 2.1% to 6.4%. The proportion of genotype 4 treatment naïve infections remained stable with 17.2% in 2001 and 18.0% in 2013. Figure 3C shows the distribution of HIV transmission risk groups among SHCS participants with a replicating HCV infection. The proportion of IDUs among participants with HCV RNA positive infections decreased from 73.2% in 2001 to 63.9% in 2013, heterosexuals remained almost stable with 15.1% in 2001 and 18.4% in 2013, whereas the proportion of MSM increased from 6.1% to 14.2%.

Characteristics of patients with replicating HCV infection in 2013

By the end of 2013, 869/2107 (41.2%) HCV RNA positive participants seen between 2000 and 2013 had replicating HCV infection: 699 were treatment naïve, 60 relapsers, and 110 non-responders. Genotype distribution was: 1, 384 (44.2%); 2, 24 (2.8%); 3, 161 (18.5%); 4, 174 (20.0%); other/unknown, 126 (14.5%). FIB-4 was >3.25 in 123 (14.2%) and APRI >1.5 in 173 (19.9%) of all patients. In 408 participants with available biopsy or transient elastography 81 (19.9%) had F2 fibrosis, 40 (9.8%) advanced liver fibrosis F3 in, and 65 (15.9%) cirrhosis F4. Most of the participants, 561 (64.6%), were IDU, 162 (18.6%) heterosexuals, and 118 (13.6%) MSM (Figure 3).

DISCUSSION

This is one of the largest nationwide community-based HIV cohort studies describing the long-term changes in epidemiology, treatment uptake, efficacy, and mortality of HCV-coinfection since the availability of HCV treatment. We found that of 12,401 cohort participants 24% were HCV-seropositive and 17% were HCV RNA positive. Of those with replicating HCV-infection, 30% were treated and 15% were cured during a follow-up period of thirteen years. During the observation period 16% of participants with active HCV-infection died, 59% due to extrahepatic complications. 41% remained with replicating HCV-infection. Taken together, only a minority of HCV-infected participants benefited from HCV therapy in the last two decades while a large part of patients still awaits treatment. By the end of 2013, 14 to 20% of coinfected individuals had advanced fibrosis or cirrhosis and thus an urgent indication for therapy; 20% of participants are treatment experienced and may thus be more difficult to cure even with DAA therapies. However, most patients did not die from liver-related complications, irrespective of treatment history. This indicates the

importance of integrative care of HIV/HCV-coinfected individuals including the diagnosis and treatment of somatic and psychiatric disorders.

The incidence of treatment uptake of 5.8 per 100 PY and a treatment rate of 30% in the SHCS is similar to recent data from other European cohorts. In the EuroSIDA study treatment incidence ranged between 2.22 and 5.93/100 PY between 2001 and 2010 [16], and in a German and Swedish HIV/HCV cohort treatment rates were 40% and 25%, respectively [17, 18]. In a large US cohort of veterans only 12% of monoinfected patients received therapy between 2000 and 2005 [19]; in coinfected populations treatment uptake was even lower [20, 21]. Predictors for treatment uptake, including genotype 3, MSM, younger age, no psychiatric disorders and controlled HIV-infection, indicate that therapy was started in the easier-to-treat patients. This is consistent with data from other studies [7, 16, 18]. Treatment uptake over time did not change significantly in our cohort.

The overall SVR rates of 35.2% in genotypes 1 and 4, respectively 68.4% in genotypes 2 and 3 are comparable to cure rates achieved in randomized controlled trials in coinfected patients [2-4]. In genotypes 1 and 4, SVR significantly increased over time. The use of weight-based ribavirin and extended treatment duration after 2008 together with increased provider experience might have resulted in higher cure rates in the more difficult-to-treat genotypes. The decision to treat after the discovery of IL28B haplotype 2009 was not influenced relevantly by this parameter. In the SHCS, IL28B was determined mainly in the frame of retrospective studies [22] and was only very rarely used in clinical decision algorithms.

Mortality was 16% in our HIV/HCV-coinfected cohort. This is comparable to the mortality rate of 14% in a US hepatitis C cohort with 3% coinfected patients [23]. SVR was strongly associated with lower mortality rates in comparison to treated patients with failure. This is in accordance with recent studies finding a reduction of mortality

and liver-related events in successfully treated patients [5, 24, 25]. In HCV-untreated patients risk of death was significantly higher compared to HCV-treated and HIV-monoinfected patients, and also significantly higher compared to treated patients with failure (Figure 2). Only about 40% of deaths were liver-related in this group, in line with data from other HIV/HCV cohorts with high extrahepatic mortality rates [23, 26]. The reason for high mortality among untreated patients may be associated with the fact that they mainly belonged to the IDU transmission group, more likely currently injected drugs, reported severe alcohol use, and had less well controlled HIV-infection (Table 1). This indicates also that this group may be generally more challenging to treat. These findings underscore the important contribution of social, behavioral and clinical factors associated with increased mortality in HIV/HCV-coinfected patients [23]. Therefore, although curing HCV is an important achievement in the care of these patients, addressing somatic and psychiatric comorbidities is key to reducing mortality in this population.

The proportion of the heterosexual HIV transmission group among patients with active HCV infection remained approximately stable in the last 13 years, whereas the percentage of IDUs decreased and that of MSM increased. The decrease in the proportion of IDUs can be attributed to successful preventive interventions including methadone substitution and needle exchange programs reducing HCV transmission in this population. Although MSM were more likely to be treated compared to patients from other transmission groups their proportion clearly increased reflecting the rise of incident HCV-infections in MSM in the SHCS which has been previously shown [27]. Despite the increased probability of HCV genotype 3 infected patients to start therapy, the distribution of genotypes did not change noticeably over time.

Major strengths of this study include the large number of patient-years with prospectively collected laboratory and clinical data, regular HCV-screening, and a

long follow-up time. Furthermore, the study provides information to physicians and public health authorities on the most urgent needs when planning future HCV interventions in a nation-wide representative community based cohort of HIV-infected patients. Our study has several limitations. We did not capture information on contraindications and adverse events of HCV treatment as a reason for deferring therapy or early treatment stop. Another limitation is the lack of vital status information of patients who left the cohort because of very restrictive legislation about linkage with death registries in Switzerland. To account for this limitation we have applied analyses with drop-out as competing risk.

In summary, the long-term assessment of HCV treatment uptake and outcome in this large HIV/HCV-coinfected population revealed a low treatment uptake, which did not increase over time. Treatment efficacy was comparable to results of randomized trials. However, due to the high mortality rate, the number of patients who died was similar to the number of patients who were cured from HCV infection during follow-up. Most deaths were not liver-related and mortality rate was significantly higher in those who did not start treatment compared to those with treatment failure, indicating that diseases other than HCV are important risk factors for mortality in these patients. By the end of 2013, a large number of HCV-coinfected SHCS participants remain to be treated. Oral DAA therapies with better tolerability, shorter treatment duration and significantly higher efficacy will allow treating many of the difficult–to-treat patients. Interferon-free DAA therapies could overcome most of the treatment barriers identified in our study (Table 2), including non-3 genotypes, higher age, IDU, low CD4 cell counts and psychiatric disorders. Within the next few years, the extent of the impact of the new treatments on the burden of liver disease in the coinfected population remains to be defined. In this context, our findings underscore the importance of efforts for optimizing care of comorbidities in HIV/HCV-coinfected

patients, given that curing HCV alone is not sufficient to achieve mortality rates similar to HIV-monoinfected patients.

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The members of the SHCS are: Aubert V, Battegay M, Bernasconi E, Böni J, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H, Fux CA, Gorgievski M, Günthard H, Haerry D, Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos R, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Metzner K, Müller N, Nadal D, Nicca D, Pantaleo G, Rauch A, Regenass S, Rickenbach M, Rudin C, Schöni-Affolter F, Schmid P, Schüpbach J, Speck R, Tarr P, Telenti A, Trkola A, Vernazza P, Weber R, Yerly S.

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Table 1: Characteristics of HIV/HCV-coinfected cohort participants at date of last follow-up visit or HCV treatment uptake, 2001-2013.

		Total	Untreated	Treated	P-value
No. of patients		2107	1471	636	
Male gender (%)		1447 (68.7)	971 (66.0)	476 (74.8)	<0.001
Median age at registration	years (IQR)	33 (28-38)	33 (28-38)	32 (28-38)	0.4
HIV transmission group (%)	MSM	249 (11.8)	138 (9.4)	111 (17.5)	<0.001
	IDU	1454 (69.0)	1056 (71.8)	398 (62.6)	
	Heterosexual	343 (16.3)	244 (16.6)	99 (15.6)	
	Other	61 (2.9)	33 (2.2)	28 (4.4)	
HCV genotype (%)	1	910 (43.2)	637 (43.3)	273 (42.9)	<0.001
	2	57 (2.7)	41 (2.8)	16 (2.5)	
	3	534 (25.3)	288 (19.6)	246 (38.7)	
	4	334 (15.9)	264 (18.0)	70 (11.0)	
	Other/unknown	272 (12.9)	241 (16.4)	31 (4.9)	
HCV RNA	≥800'000 IU/ml	1019 (48.4)	678 (46.1)	341 (53.6)	<0.001
	<800'000 IU/ml	1017 (48.3)	732 (49.8)	285 (44.8)	
	Unknown	71 (3.4)	61 (4.2)	10 (1.6)	
ALT, U/L	median (IQR)	45 (27-80)	45 (27-74)	45 (25-102)	0.6
AST U/L	median (IQR)	43 (30-72)	43 (30-69)	43 (27-80)	0.9
Platelet count (k/µL)	median (IQR)	197 (154-253)	199 (157-256)	191 (140-237)	0.08
FIB-4	available, n (%)	623 (29.6)	458 (31.1)	165 (25.9)	
	median (IQR)	1.26 (0.8-2.1)	1.23 (0.9-2.0)	1.33 (0.8-2.2)	0.6
	>3.25, n (%)	72 (11.6)	48 (10.5)	24 (14.6)	0.3
APRI	available, n (%)	623 (29.6)	458 (31.1)	165 (25.9)	
	median (IQR)	0.47 (0.3-0.9)	0.46 (0.3-0.8)	0.54 (0.3-0.9)	0.2
	>1.5, n (%)	126 (20.2)	86 (18.8)	40 (24.4)	0.02
Fibrosis score (Fibroscan, biopsy)	available, n (%)	764 (36.3)	389 (26.4)	375 (59.0)	

	Metavir ≥F3	253 (33.1)	74 (19.0)	179 (47.7)	<0.001
CD4 cells/µl	median (IQR)	449 (287-651)	447 (273-659)	451 (312-616)	0.7
	≤200 cells/µl, n (%)	298 (14.1)	245 (16.7)	53 (8.3)	<0.001
On ART	all	1574 (74.7)	1038 (70.6)	536 (84.3)	<0.001
	HIV RNA undetectable	1370 (87.0)	887 (85.5)	483 (90.1)	0.009
Hepatitis B infection		112 (5.3)	76 (5.2)	36 (5.7)	0.6
Psychiatric disorder		430 (20.4)	330 (22.4)	100 (15.7)	<0.001
Opiate maintenance program		864 (41.0)	703 (47.8)	161 (25.3)	<0.001
Active intravenous drug use		306 (14.5)	255 (17.3)	51 (8.0)	<0.001
Severe alcohol abuse		281 (13.3)	208 (14.1)	73 (11.5)	<0.001
Type of health care provider	University center	1299 (61.7)	932 (63.3)	367 (57.7)	0.003
	Affiliated hospital	243 (11.5)	176 (12.0)	67 (10.5)	
	Private physician	565 (26.8)	363 (24.7)	202 (31.8)	
Treating time period	2001-2004			197 (31.0)	
	2005-2007			164 (25.8)	
	2008-2010			150 (23.6)	
	2011-2013			125 (19.7)	

*p-values were calculated by Fisher's exact tests for categorical and Wilcoxon rank-sum tests for continuous variables.
Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, intravenous drug user; IQR, interquartile range; MSM, men who have sex with men.

Table 2: Uni- and multivariable Poisson regression models for predictors associated with hepatitis C virus (HCV) treatment uptake in the SHCS, 2001-2013.

		Univariable Analysis		Multivariable Analysis	
		IRR (95% C.I.)	P-value	IRR (95% C.I.)	P-value
Age group, years	16-29	Ref.		Ref.	
	30-39	0.61 (0.41-0.91)	0.02	0.63 (0.42-0.95)	0.03
	40-49	0.63 (0.43-0.92)	0.02	0.63 (0.42-0.94)	0.03
	>49	0.41 (0.27-0.63)	<0.001	0.35 (0.22-0.54)	<0.001
HIV transmission group (%)	MSM	Ref.		Ref.	
	Heterosexual, female	0.29 (0.20-0.42)	<0.001	0.25 (0.17-0.36)	<0.001
	Heterosexual, male	0.44 (0.32-0.61)	<0.001	0.37 (0.27-0.52)	<0.001
	IDU, female	0.28 (0.22-0.37)	<0.001	0.21 (0.16-0.28)	<0.001
	IDU, male	0.38 (0.30-0.48)	<0.001	0.29 (0.22-0.36)	<0.001
	Other	0.58 (0.38-0.89)	0.01	0.42 (0.27-0.64)	<0.001
HCV genotype (%)	1	Ref.		Ref.	
	2	0.94 (0.57-1.55)	0.8	0.97 (0.58-1.61)	0.9
	3	1.83 (1.53-2.18)	<0.001	2.03 (1.70-2.42)	<0.001
	4	0.64 (0.49-0.83)	0.001	0.62 (0.47-0.81)	0.001
	Other/unknown	0.61 (0.42-0.90)	0.01	0.45 (0.30-0.67)	<0.001
HCV RNA	≥800'000 IU/ml	Ref.		Ref.	
	<800'000 IU/ml	0.91 (0.78-1.06)	0.2	0.92 (0.78-1.08)	0.3
CD4 cell count, cells/µl	<200	Ref.		Ref.	
	200-349	1.80 (1.30-2.49)	<0.001	1.79 (1.29-2.49)	0.001
	≥350	1.31 (0.98-1.76)	0.07	1.40 (1.03-1.91)	0.03
Not on ART		Ref.		Ref.	
On ART with detectable HIV RNA		1.12 (0.80-1.57)	0.5	1.15 (0.82-1.63)	0.4
with undetectable HIV RNA		1.06 (0.85-1.33)	0.6	1.00 (0.80-1.26)	1.0
Psychiatric disorder	No	Ref.		Ref.	
	Yes	0.65 (0.53-0.81)	<0.001	0.67 (0.54-0.83)	<0.001
Type of health care provider	University center	Ref.		Ref.	
	Affiliated hospital	0.83 (0.64-1.08)	0.2	0.83 (0.64-1.08)	0.2
	Private physician	1.26 (1.05-1.50)	0.01	1.24 (1.04-1.49)	0.02
Treating time period	2001-2004	Ref.		Ref.	
	2005-2007	0.78 (0.63-0.97)	0.02	0.84 (0.68-1.03)	0.10
	2008-2010	0.80 (0.64-0.99)	0.04	0.92 (0.73-1.14)	0.4

	2011-2013	0.92 (0.73-1.15)	0.5	1.17 (0.91-1.49)	0.3

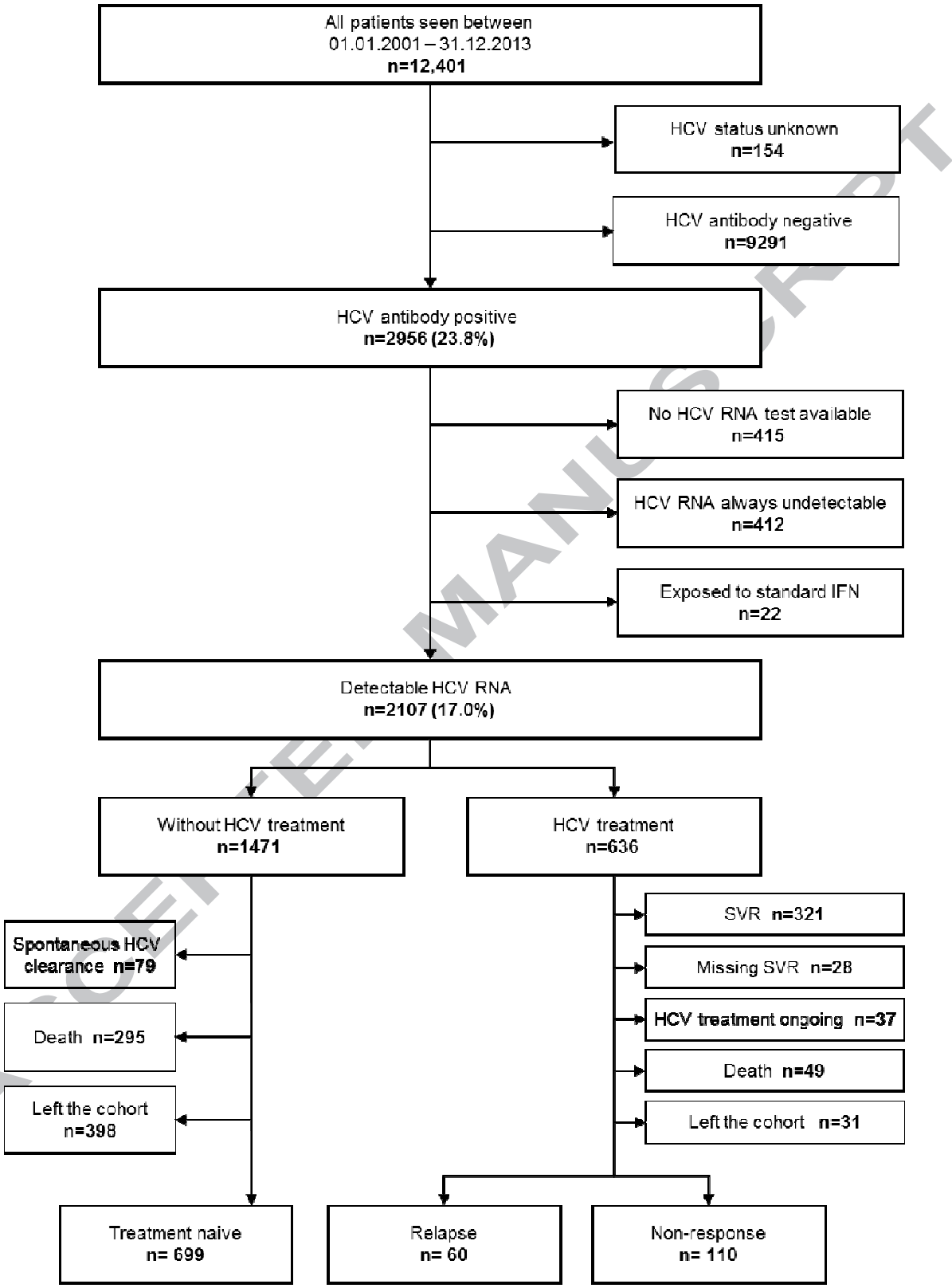
Abbreviations: ART, antiretroviral therapy; HCV, hepatitis C virus; IDU, intravenous drug user; MSM, men who have sex with men.

Supplementary Table 1: Characteristics of HIV-monoinfected, HCV-coinfected untreated and treated participants at date of first visit after 1.1.2001 to 2013.

		HCV negative	HCV untreated	HCV treated	P-value*
No. of patients		9291	1471	636	
Male gender (%)		6689 (72.0)	971 (66.0)	476 (74.8)	<0.001
Median age at last visit	years (IQR)	39 (33-46)	38 (34-43)	39 (35-42)	0.005
HIV transmission group (%)	MSM	4548 (49.0)	138 (9.4)	111 (17.5)	<0.001
	IDU	160 (1.7)	1056 (71.8)	398 (62.6)	
	Heterosexual	4125 (44.4)	244 (16.6)	99 (15.6)	
	Other	458 (4.9)	33 (2.2)	28 (4.4)	
CD4 cells/µl	median (IQR)	404 (248-591)	357 (220-559)	408 (257-593)	<0.001
Ever on ART (%)		8768 (94.4)	1373 (93.3)	620 (97.5)	0.001
Ever AIDS (%)		2151 (23.2)	432 (29.4)	172 (27.0)	<0.001

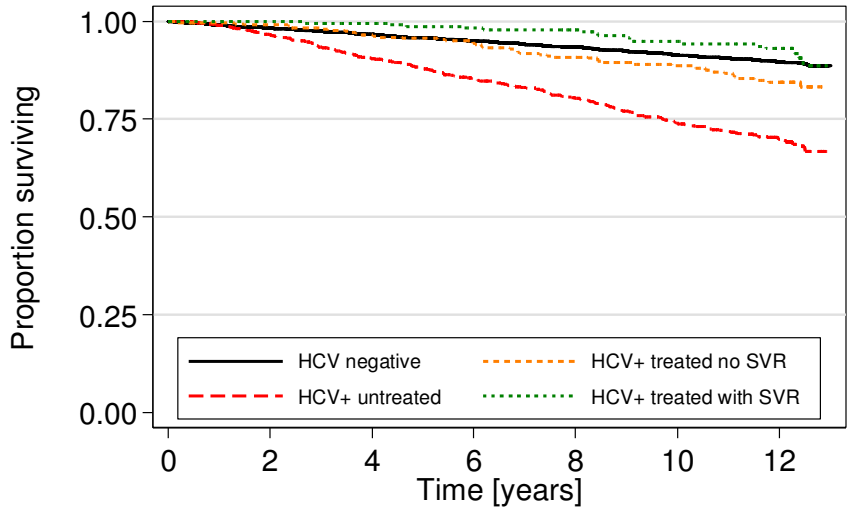
*p-values were calculated by Fisher's exact tests for categorical and Wilcoxon rank-sum tests for continuous variables.
Abbreviations: ART, antiretroviral therapy; HCV, hepatitis C virus; IDU, intravenous drug user; IQR, interquartile range; MSM, men who have sex with men.

Figure 1: Patient Flowchart



Abbreviations: HCV, hepatitis C virus; IFN, interferon; SVR, sustained viral response.

Figure 2: Kaplan-Meier survival curve of HCV-coinfected untreated, treated, and HIV-monoinfected SHCS participants.

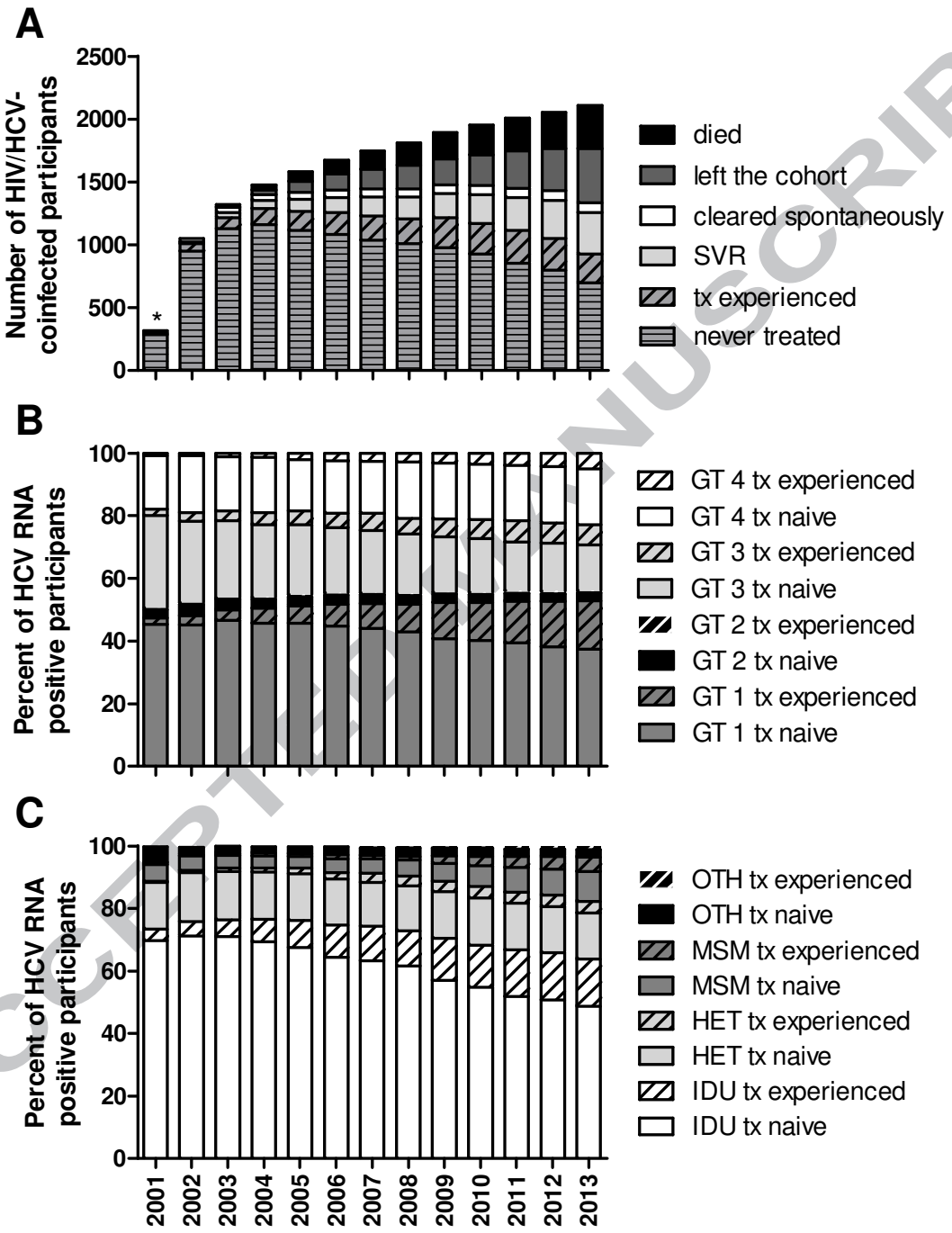


Numbers at risk:

HCV negative	9291	5113	2184
HCV+ untreated	1471	815	345
HCV+ treated no SVR	374	300	162
HCV+ treated with SVR	262	224	124

Abbreviations: HCV, hepatitis C virus; SVR, sustained viral response.

Figure 3: **A)** Distribution of HCV-coinfected SHCS participants by HCV treatment status, 2001-2013. **B)** Distribution of HCV RNA positive SHCS participants by HCV genotype, 2001-2013 (7.5% unknown genotypes are not included). **C)** Distribution of HCV RNA positive SHCS participants by HIV transmission group, 2001-2013.



*) HCV RNA was regularly measured after 2001.
Abbreviations: GT, genotype; OTH, other HIV transmission group; HET, heterosexuals; IDU, intravenous drug user; MSM, men who have sex with men; SVR, sustained viral response; tx, treatment.